At page 10, delete and replace paragraph [0032] as shown in the attached marked-up and clean copies.

At page 10, delete and replace paragraph [0034] as shown in the attached marked-up and clean copies.

At page 16, delete and replace paragraph [0073] as shown in the attached marked-up and clean copies.

At page 18, delete and replace paragraph [0078] as shown in the attached marked-up and clean copies.

At page 18, delete and replace paragraph [0079] as shown in the attached marked-up and clean copies.

At pages 18 and 19, delete and replace paragraph [0080] as shown in the attached marked-up and clean copies.

At page 19, delete and replace paragraph [0081] as shown in the attached marked-up and clean copies.

At pages 19 and 20, delete and replace paragraph [0082] as shown in the attached marked-up and clean copies.

REMARKS

Applicants note that figure reference “Figure 2A” in the informal drawings is now “Figures 2A and 2A-1” in the formal drawings. Applicants also note that figure reference “Figure 3” in the informal drawings is now “Figures 3A and 3B” in the formal drawings. These changes were made to comply with stylistic requirements for formal drawings. Accordingly, Applicants submit that the formal drawings and amendments requested herein add no new matter and respectfully request entry of the formal drawings and amendments.

Respectfully submitted,

Date: July 3, 2002
Reg. No. 47,411

Tel. No.: (617) 248-7102
Fax No.: (617) 248-7100

Michael J. Bastian
Attorney for Applicant
Testa, Hurwitz, & Thibeault, LLP
High Street Tower
125 High Street
Boston, Massachusetts 02110

2445303_1

CLEAN COPY OF REPLACEMENT PARAGRAPHS

A1

[0032] Figures 2A and 2A-1 depict human cervix tissue and show an area of which a sequence of images are to be obtained according to an illustrative embodiment of the invention.

A2

[0034] Figures 3A and 3B show a series of graphs depicting mean signal intensity of a region as a function of time, as determined from a sequence of images according to an illustrative embodiment of the invention.

A3

[0073] Figures 2A, 2A-1, and 2B relate to step 102 of Figure 1, obtaining a sequence of images of the tissue. Although embodiments of the invention are not limited to aceto-whitening tests, an exemplary sequence of images from an aceto-whitening test performed on a patient is used herein to illustrate certain embodiments of the invention. Figure 2A depicts a full-frame image 202 of a human cervix after application of acetic acid, at the start of an aceto-whitening test. The inset image 204 depicts an area of interest to be analyzed herein using embodiment methods of the invention. This area of interest may be determined by a technician or may be determined in a semi-automated fashion using a multi-step segmentation approach such as one of those discussed herein below.

A4

[0078] Figures 3A and 3B relate to part of step 104 of Figure 1, preprocessing the images. Figures 3A and 3B show a series of graphs depicting mean signal intensity 304 of a pixel as a function of time 306, as determined from a sequence of images according to an illustrative embodiment of the invention. The graphs depict application of a morphological filter, application of a diffusion filter, modification of intensity data to account for background intensity, and normalization of intensity data, according to an illustrative embodiment of the invention.

[0079] According to the illustrative embodiment, a first filter is applied to the time axis, individually for each pixel. The images are then spatially filtered. Graph 302 of Figure 3A depicts the application of both a temporal filter and a spatial filter at a representative pixel. The original data is connected by a series of line segments 308. It is evident from graph 302 that noise makes the signal choppy and adversely affects further analysis if not removed.

A4 contd

A4 cont'd

[0080] For temporal filtering, the illustrative embodiment of the invention applies the morphological filter of Equation (3):

$$w(t) \odot b = \frac{1}{2}\left[(w \circ b) \bullet b + (w \bullet b) \circ b\right], \qquad (3)$$

where b is the *structuring element*, $\circ$ is the *opening* operator, and $\bullet$ is the *closing* operator. According to the illustrative embodiment, the structuring element has a half circle shape. The temporally-filtered data is connected by a series of line segments 310 in the graph 302 of Figure 3A. The noise is decreased from the series 308 to the series 310.

[0081] Illustratively, the images are then spatially filtered, for example, with either an isotropic or a Gaussian filter. A diffusion equation implemented by an illustrative isotropic filter may be expressed as Equation (4):

$$\frac{\partial w(i,j)}{\partial \tau} = k\nabla \cdot \nabla w = k\Delta w \quad , \qquad (4)$$

where ∇ is the gradient operator, Δ is the Laplacian operator, and τ is the diffusion time (distinguished from the time component of the whitening signal itself). An isotropic filter is iterative, while a Gaussian filter is an infinite impulse response (IIR) filter. The iterative filter of Equation (4) is much faster than a Gaussian filter, since the iterative filter allows for increasing smoothness by performing successive iterations. The Gaussian filter requires re-applying a more complex filter to the original image for increasing degrees of filtration. According to the illustrative embodiment, the methods of the invention perform two iterations. However, in other embodiments, the method performs one iteration or three or more iterations. The spatially-filtered data for a representative pixel is connected by a series of line segments 312 in graph 302 of Figure 3A. The noise is decreased from series 310 to series 312.

[0082] Graph 314 of Figure 3B shows the application of Equation (2), background subtracting the intensity signal 304. Graph 318 of Figure 3B shows the intensity signal data following normalization 320. In the illustrative embodiment, as explained below in further detail, normalization includes division of values of the intensity signal 304 by a reference value, such as the maximum intensity signal over the sequence of images. Glare and chromatic artifacts can affect selection of the maximum intensity signal; thus, in an illustrative embodiment, normalization is performed subsequent to correcting for glare and chromatic artifacts.

A4 concl'd

MARKED-UP COPY OF REPLACEMENT PARAGRAPHS

[0032] Figures 2A and 2A-1 depict[s] human cervix tissue and show[s] an area of which a sequence of images are to be obtained according to an illustrative embodiment of the invention.

[0034] Figures 3A and 3B show[s] a series of graphs depicting mean signal intensity of a region as a function of time, as determined from a sequence of images according to an illustrative embodiment of the invention.

[0073] Figures 2A, 2A-1, and 2B relate to step 102 of Figure 1, obtaining a sequence of images of the tissue. Although embodiments of the invention are not limited to aceto-whitening tests, an exemplary sequence of images from an aceto-whitening test performed on a patient is used herein to illustrate certain embodiments of the invention. Figure 2A depicts a full-frame image 202 of a human cervix after application of acetic acid, at the start of an aceto-whitening test. The inset image 204 depicts an area of interest to be analyzed herein using embodiment methods of the invention. This area of interest may be determined by a technician or may be determined in a semi-automated fashion using a multi-step segmentation approach such as one of those discussed herein below.

[0078] Figures 3A and 3B relate[s] to part of step 104 of Figure 1, preprocessing the images. Figures 3A and 3B show[s] a series of graphs depicting mean signal intensity 304 of a pixel as a function of time 306, as determined from a sequence of images according to an illustrative embodiment of the invention. The graphs depict application of a morphological filter, application of a diffusion filter, modification of intensity data to account for background intensity, and normalization of intensity data, according to an illustrative embodiment of the invention.

[0079] According to the illustrative embodiment, a first filter is applied to the time axis, individually for each pixel. The images are then spatially filtered. Graph 302 of Figure 3A depicts the application of both a temporal filter and a spatial filter at a representative pixel. The original data is connected by a series of line segments 308. It is evident from graph 302 that noise makes the signal choppy and adversely affects further analysis if not removed.

[0080] For temporal filtering, the illustrative embodiment of the invention applies the morphological filter of Equation (3):

$$\mathrm{w}(t) \odot b = \frac{1}{2}\left[(\mathrm{w} \circ b) \bullet b + (\mathrm{w} \bullet b) \circ b\right], \qquad (3)$$

where b is the *structuring element*, $\circ$ is the *opening* operator, and $\bullet$ is the *closing* operator. According to the illustrative embodiment, the structuring element has a half circle shape. The temporally-filtered data is connected by a series of line segments 310 in the graph 302 of Figure 3A. The noise is decreased from the series 308 to the series 310.

[0081] Illustratively, the images are then spatially filtered, for example, with either an isotropic or a Gaussian filter. A diffusion equation implemented by an illustrative isotropic filter may be expressed as Equation (4):

$$\frac{\partial \mathrm{w}(i,j)}{\partial \tau} = k\nabla \cdot \nabla \mathrm{w} = k\Delta \mathrm{w} \quad , \qquad (4)$$

where ∇ is the gradient operator, Δ is the Laplacian operator, and τ is the diffusion time (distinguished from the time component of the whitening signal itself). An isotropic filter is iterative, while a Gaussian filter is an infinite impulse response (IIR) filter. The iterative filter of Equation (4) is much faster than a Gaussian filter, since the iterative filter allows for increasing smoothness by performing successive iterations. The Gaussian filter requires re-applying a more complex filter to the original image for increasing degrees of filtration. According to the illustrative embodiment, the methods of the invention perform two iterations. However, in other embodiments, the method performs one iteration or three or more iterations. The spatially-filtered data for a representative pixel is connected by a series of line segments 312 in graph 302 of Figure 3A. The noise is decreased from series 310 to series 312.

[0082] Graph 314 of Figure 3B shows the application of Equation (2), background subtracting the intensity signal 304. Graph 318 of Figure 3B shows the intensity signal data following normalization 320. In the illustrative embodiment, as explained below in further detail, normalization includes division of values of the intensity signal 304 by a reference value, such as the maximum intensity signal over the sequence of images. Glare and chromatic artifacts can affect selection of the maximum intensity signal; thus, in an illustrative embodiment, normalization is performed subsequent to correcting for glare and chromatic artifacts.